been added. Claim 24 has not been amended to overcome prior art. The full doctrine of equivalents applies to all claim elements. Accordingly, withdrawal of the Section 112 rejection is respectfully requested.

From the Examiner's comments regarding the prior art rejections, it is clear that the claimed creation of **supersaturated** emulsions (i.e. producing emulsions which contain a drug concentration being well above the maximum soluble combined amount of the water and the oil phase) and the exclusion of organic solvents was overlooked.

Oil and water emulsions have been used since the seventies to deliver drugs intravenously. The drugs are typically dissolved in the oil of the emulsion, such as the presently cited Kaufmann. Kaufmann even uses solvents to facilitate dissolution in the oils. Alternatively drugs can be incorporated via a lecithin blend using organic solvents. The present invention does not use organic solvents, and therefore the product is organic solvent-free. In contrast, Kaufmann contains organic solvent residues.

A further obstacle for many drugs is the poor solubility in water and simultaneously in oils. A typical example is Amphotericin B. The limitation in solubility leads to undesirably large injection volumes, or in many cases reaches volumes too large to be administered to a patient. An example is the maximum solubility of Amphotericin B (1mg/mL) in the o/w emulsion, such as in the presently cited Davis. The present invention allows the incorporation of drugs in concentrations above the saturation solubility of the drug in the emulsion (total solubility = amount of drug in water plus amount of drug in oil). The present invention allows one to reach supersaturation in the emulsions, i.e. going beyond the previously known maximum solubilities. For example, instead of 1 mg/ml (maximum solubility in oil/water), the incorporated amount can now be doubled to a concentration of 2mg/ml (supersaturation). In variants of the invention, concentrations of 5-10mg/mL can even be achieved. None of the cited references anticipates, teaches or suggests such supersaturation or formation of drugs that are organic solvent-free.

The rejection of claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) as being anticipated by EPO 0 296 845 (Davis) is respectfully traversed. The claimed invention is not anticipated by Davis for the following reasons.

The Examiner summarizes correctly the emulsion produced according to Davis in that an emulsion system containing a poorly soluble drug for parenteral administration is produced.

The first difference to the present invention is that Davis is using organic solvents. Consequently even after removal of the solvent by classical, well-known means a residue of solvent will remain in the emulsion, which can cause toxicological problems and even may prevent registration with the authorities in case the contamination level is too high. In addition, removal of the organic solvent is a costly process. The product of the invention is organic solvent-free because no organic solvents are used in the production process. This is pointed out in claim 1 as characteristic feature of the product. The product by Davis always contains solvent residues, even when they are only in the lower ppm concentration range.

According to Davis a concentration of 0.5 mg/l can be achieved when using 1.2% lecithin and 10% soya oil in the emulsion (90ml mixture of water, lecithin and drug plus 10 ml oil, Example 1). The loading can be increased to 1 mg/ml when increasing the lecithin to 1.8% and the oil to 20%. These concentrations represent the maximum amount of drug being soluble in the oil and water phase, i.e. the saturation solubility of the drug in these emulsions.

In contrast, the present invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion. Even when using only 1.2% lecithin, the present invention can incorporate 2mg/ml Amphotericin B. The present invention can use a concentration above the saturation solubility and double the amount which can be achieved by Davis even when using the higher lecithin concentration of 1.8%.

The present invention creates supersaturated emulsions, which are not disclosed in Davis. On the contrary, Davis teaches clear limits for the maximum drug incorporation.

According to the present invention, it is surprisingly possible to enter the supersaturated concentration range without precipitation of drug crystals during storage. This is achieved by the novel production technology discovered and disclosed in the present application, i.e. co-homogenisation of drug powder and oil in water.

In view of the many differences between Davis and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) as being anticipated by U.S. patent No. 5,616,330 (Kaufman) is respectfully traversed. The claimed invention is not anticipated by Kaufman for the following reasons.

Kaufmann also uses organic solvents to dissolve the drug, which means the emulsion will also have at least residues of organic solvents. The present invention is free of organic solvents.

In addition, Kaufmann prepares only an emulsion with a drug concentration being soluble in the oil phase of the emulsion (due to the poor solubility of paclitaxel in the water phase, this amount can be ignored). This emulsion is not a supersaturated system. The present invention can go beyond the maximum concentration soluble in the oil phase to provide a supersaturated concentration range.

In view of the many differences between Davis and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-15, 19-66, 143, 144, 146 and 148 under 35 U.S.C. § 103 as being unpatentable over Davis alone or Kaufman alone is respectfully traversed. The claimed invention is not taught or suggested by either of Davis or Kaufman for the following reasons.

Davis:

The Examiner essentially argues on pages 5-6 of the Office Action that known emulsions using similar compositions of excipients can be administered by the same routes and have similar sizes. However, this does not apply to drugs for the reasons discussed below.

On page 7, 2nd paragraph of the Office Action, the Examiner denies any significant distinction between Davis and the present invention. A main difference overlooked by the Examiner is the achieved drug loading: (1) the saturation concentration with Davis and Kaufmann; and (2) in the supersaturation range in the present invention.

According to the Examiner, Davis teaches similar amounts of drug incorporated in the suspension compared to the present invention (page 7, last paragraph of Office Action). Davis discloses up to 1 mg/ml, preferably 0.5mg/ml of Amphotericin (column 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water. In the present invention, going beyond this saturation limit and even doubling the saturation solubility is unexpected and something which was not predictable from Davis. Davis does not teach supersaturation of drugs. The instant invention can, for example, produce emulsions with 5mg/ml Amphotericin (supersaturated), Davis cannot.

Applicant believes the invention works in the following manner but is not bound by this theory. Applicant's belief about the mechanism have been submitted for publication to the Int. J. Pharm. The drug is believed to be not molecularly dispersed in the lecithin layer, and it seems to form "molecular nano-arrangements", which allow a much higher drug incorporation than molecular dissolution in the lecithin. These special arrangements in the interfacial layer are generated by the novel production method disclosed in the present application. It is speculated that the high energy input in the presence of a high drug concentration leads to the formation of such nanostructures and increased loading capacity. Previously, homogenization with such high drug concentration was not tried because it appeared to be nonsense. It was expected that drug concentrations above the saturation solubility in the emulsion could not be incorporated and would remain as sediment. Just the opposite was surprisingly found in the instant invention.

Applicant respectfully submits that the Examiner is not correct when in stating that "the prior art teaches suitable concentration to arrive at stable emulsions." The prior art concentrations are not sufficiently high to obtain acceptable injection

volumes. The previous emulsions are at the or even below the saturation concentration, i.e. they are not supersaturated emulsions. The emulsions of the invention are also stable, but the key feature is the supersaturation, which provides suitable injection volumes.

Kaufmann:

The Examiner points out the different excipients used by Kaufmann and also the differnt taxines. Kaufmann teaches the amount of 0.1% to 1% taxine in the emulsions which, according to the Examiner, are in the range of the present invention.

However, one cannot compare incorporation of one drug (Amphotericin) directly with another drug (in this case taxine). It might be easy to incorporate drug A (e.g. taxine) in a concentration of 1% in case the saturation solubility in the emulsion is well above, e.g. 5%. However, even when incorporating 1% of drug B, this represents a major achievement when the saturation solubility of B is only e.g. 0.1%. From this, direct comparison on the basis of just percentages is not possible. The solubility of each drug must also be considered.

Furthermore, according to the present invention, concentrations of 5 and 10mg/ml can be incorporated, the latter by using an emulsion with crystalline fraction.

In addition, Kaufmann clearly teaches using Cholesterol to solubilize the drug. This means that Kaufmann is working with an oil phase <u>at the maximum solubility</u>. The instant invention is working well above the saturation solubilities. In contrast to Kaufmann, the present invention is a <u>supersaturated</u> system.

As discussed above, the supersaturated system according to the present invention is unexpected and provides many advantages over the conventional maximum solubility system of Kaufmann.

Furthermore, both Davis and Kaufmann teach using organic solvents, which are excluded by the present invention. There is no teaching in either reference to exclude the use of organic solvents.

In view of the many differences between the present invention and Davis or Kaufmann, and the many unexpected advantages of the present invention, withdrawal of the Section 103 rejection is respectfully requested.

In view of all of the rejections of record having been addressed, Applicant believes the application to be in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
Manelli Denison & Selter PLLC

By _____

Jeffrey S. Melcher
Reg. No.: 35,950
Tel. No.: (202) 261-1045
Fax. No.: (202) 887-0336

Customer No. 20736